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CHEMICAL & ENGINEERING NEWS

C&EN

SEPTEMBER 28, 1992

ASIA'S RAPID CHEMICAL DEVELOPMENT POSES CHALLENGES TO WEST PAGE 23

CHIRAL DRUGS

A "Chirotechnology" Industry Emerges
Page 46

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CHEMICAL & ENGINEERING NEWS

C&EN

SEPTEMBER 28, 1992

NEWS OF THE WEEK

■ Taking an unprecedented step in continuing battle over "pork-barrel science," House votes to deny funding earmarked for 10 academic research facilities in an appropriation bill. Page 6

■ Biochemist Bruce M. Alberts has been nominated to be the next president of the National Academy of Sciences. Page 7

■ Currency turmoil sweeping Europe may have overall positive effects for the European chemical industry. Page 7

■ Technology and future innovations are the emphasis of a science competition for precollege students that was launched last week by the National Science Teachers Association and Japan's Toshiba Corp. Page 8

■ Publishers Elsevier and Reed International have agreed to merge next Jan. 1, forming one of the world's largest scientific publishing companies. Page 8

COVER: Drawings of two enantiomers, D- and L-glyceraldehyde, by Tripos Associates, St. Louis, using molecular modeling program Sybyl

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LETTERS

Future job market in chemistry

I recently attended the meeting of the Committee on Professional Relations at the 204th American Chemical Society national meeting. The picture presented by the participants ranged from abject gloom to euphoria regarding the future job market. In contrast, the mood of the audience was extremely negative.

The major controversy among the speakers was the proper prediction of numbers of people in chemical employment in the 21st century. Optimistic values for the job market were based on a growth in the economy, the requirement for more teachers for the greater number of students taking high school and college chemistry (based on the projected need for scientific literacy in the workplace), and no dimunition in research funded by the government and the defense industries. Pessimistic numbers were founded on major sections of research moving overseas, greater efficiency in the research community, lower R&D support from the government, and negligible growth in the economy. Although some speakers indicated a turnaround in the current depressed job market as early as 1996, others forecasted that the change would not occur until 2005. However, all the speakers stressed that future supply-and-demand numbers were subject to major modification depending on unforeseen circumstances.

On one subject there was general agreement: Chemists are currently hurting in the job market. Terminations at major companies have essentially ended the careers of chemists in their mid-40s to early 60s with very little chance of reentry into the marketplace in either 1996 or 2005 as their skills diminish with lack of use. Decreased hiring rates in a depressed market have lowered the expectations of recent graduates and have driven them either into postdoctoral positions or into fields that require minimal chemical training. If a shortage does occur in the future, it will not be based on increased demand, but rather on a mass exodus of highly trained individuals from the chemical field who are not currently employable.

What is the responsibility of the chemical industry in the current crisis in employment? Certainly it is not to berate the colleges for not training for a specific specialization desired by the company while the same corporation simultaneously is terminating hundreds of other chemists. Rather the chemical industry, up to a certain point, has an obligation to maintain a viable, balanced research staff for future growth. To accomplish this objective, ACS must open two-way communication with the major industrial chemical companies that emphasizes the long-term destructive consequences of their short-term hiring practices.

The pain is real; the chemical profession has been reduced to a slave market for too many well-educated scientists. It is time that the rosy predictions for the future be replaced by a realistic examination of the present plight in chemical professional employment. ACS, the chemical industry, and the colleges should alert budding scientists to the degree of opportunity in the field of chemistry to reduce future disillusionment.

Nelson Marans
Silver Spring, Md.

Behavior modification

I am prompted to write this letter by a comment from one of the society's student affiliates who presented a poster paper at the San Francisco meeting. The student noted that a number of university faculty members stopped by his poster, but upon finding that he was not interested in attending their graduate program, immediately moved on to other posters. This seemed to be a fairly common occurrence at the student affiliate session. This kind of boorish behavior has no place at a student affiliate session, or, for that matter, at any session.

Undergraduates who have spent the time, effort, and money to come to a meeting represent the very best of our potential new colleagues and they deserve the same kind of personal respect as any other researcher. Not only is the behavior rude, it is also pointless. Seniors who plan to go to graduate school usually have made their decisions before the

Correction

• Sept. 21, page 6: CFC-12 is CCl_2F_2, not CH_2F_2.

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Asian chemical growth poses challenge to Western chemical firms

Earl V. Anderson,
C&EN Northeast News Bureau

Sir Denys H. Henderson, chairman of the U.K.'s ICI, notes that Columbus was actually looking for "the Orient" when he bumped into America. Today, the world's chemical industries are discovering what Columbus missed.

If there were any lingering doubts that Asia is where the action is for the chemical industry, they were thoroughly squashed at the 2nd World Chemical Congress, held recently at Newport Beach, Calif. The pattern of world chemical demand likely will change significantly during the next 10 years, and Asia will be the trigger for that change.

Henderson came to the Chemical Congress from London, but he talked only about Asia. Edward Delboy, vice president of Shell International Chemical, also came from London. He, too, emphasized Asia. Masaki Yoshida, president and chief executive officer of Mitsubishi Petrochemical, flew in from Japan. And he stressed the chemical phenomenon that is Asia.

Asia, says Henderson, will influence significantly a large part of the industry's strategic planning and business decisions. Three distinct trading blocs are emerging in the world—North America (including Mexico), an expanding Western Europe, and the Asia-Pacific region. And if any one of those three blocs is leading the way toward a different world order, it is Asia, he says.

And with good reason. Last year, the region accounted for 21% of the world's gross domestic product (GDP), up from only 13% in 1974. With the economies of Asia growing at more than twice the rate of either the U.S. or Western Europe, by the year 2000 that share will jump to 24%, says Henderson.

Henderson's growth figures exclude the former communist countries. But Mitsubishi Petrochemical's Yoshida says the three countries of Indochina—Laos, Cambodia, and Vietnam—have tremendous growth potential. Vietnam, in particular, merits special attention.

However it's measured, economic growth in Asia will be robust and will have an impact on the world chemical scene. Demand for chemicals in Asia is growing twice as fast as in the West. With only 18% of world chemical sales in 1974, Asia has boosted its share to 26% in 1990 and likely will push it up to a hefty 30% by 2000. This rapid growth has been—and will be—based on a strong buildup of the region's industrial foundation and not on agriculture, which accounts for less than 10% of GDP.

These economic tidbits indicate that Asia poses a much bigger challenge for Western companies than these firms realize, says Henderson. Chemical companies are no exception.

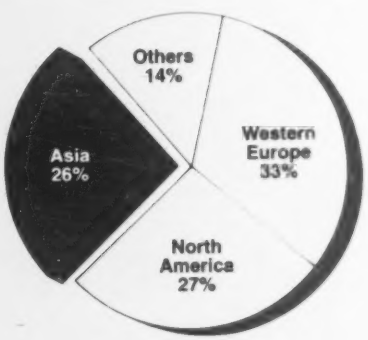
Asia currently is a net importer of chemicals. But by the end of the decade, Henderson expects it will be a net exporter. As a result, he believes Asia poses a clear threat to the chemical industries in North America and Western Europe.

The threat is twofold. Asian chemical companies first will try to satisfy new markets in their own region. This will make it much more difficult for Western chemical companies to maintain current export levels to the region. It also will make it more difficult for them to find ways of participating fully in the region's future growth. To make matters worse, Henderson says Asian chemical companies also likely will try to establish strong chemical export markets for themselves in the West.

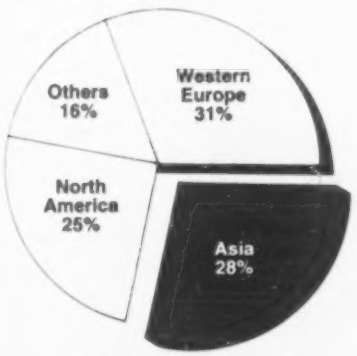
These trends are bound to have an impact on Japanese chemical companies, says Yoshida. Japanese chemical exports, which until now have helped satisfy demand throughout Asia, will be replaced by local production. When that happens, Yoshida says Japanese chemical companies, instead of maintaining current export levels for their products, will be exporting technology, capital, and management expertise to their Asian neighbors.

Shell International's Delboy agrees that Japanese chemical firms will be active in the Asia region, as far as ethylene and its derivatives are concerned. And he agrees that they will, indeed, be providing money, technology, and

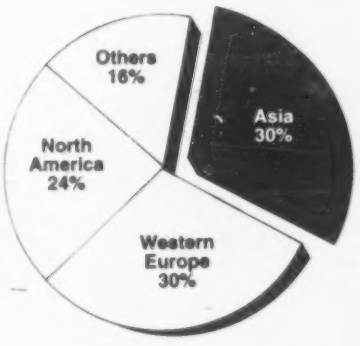
Asia is expected to account for increasing share of world chemical market



1990 world chemical market = $1.08 trillion[a]

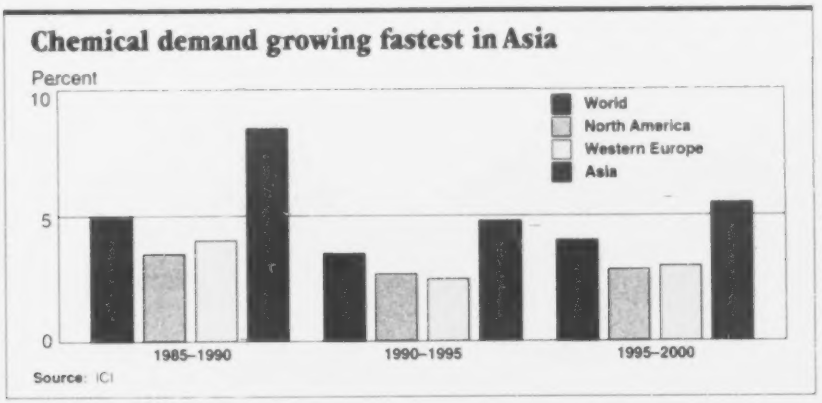


1995 world chemical market = $1.28 trillion[a]



2000 world chemical market = $1.55 trillion[a]

Note: Percentages are rounded to nearest whole number. a At 1990 prices and exchange rates. **Source:** ICI



management expertise as they globalize their activities.

Japan's big commodity trading houses will also be involved. For them, says Delboy, even minor equity investments could help secure plant and equipment contracts, feedstock supplies, and market access for their other products.

But there also will be room for other international investors—large U.S. and European firms—in the Asian ethylene picture, says Delboy. Faced with mature home markets and diminishing exports, these large Western chemical companies probably will invest overseas to maintain growth. Asia will be, or at least should be, a prime target.

International oil companies have what it takes to participate in a growing Asian petrochemical industry, says Delboy. They are experienced in investing and operating in diverse geographical areas. And 10 of the 15 largest international petrochemical companies are affiliates of oil companies.

Because they are already operating in many Asian countries, the oil companies know the region well. Local authorities also know them, which makes the oil giants attractive partners for local investors.

But there should be room for much more foreign investment in Asian ethylene projects. Delboy believes that up to 12 million metric tons of new ethylene capacity will be needed in Asia between 1990 and 2000. Depending on size and location, that huge volume means between 25 and 30 new ethylene crackers. To put that in context, the additional capacity needed in Asia represents about two thirds of Western Europe's current capacity.

Delboy estimates that a new olefins complex, including derivatives plants, costs upward of $1.5 billion at today's prices. "There would seem to be plenty of action to be had in the region," he says.

Delboy also estimates that about 40% of this new action—such as new crackers in Japan, South Korea, and some in China—will be taken by domestic players. But that still leaves about 60%, or about 7 million metric tons per year, of ethylene capacity that could be developed with major foreign involvement.

One company, at least, that isn't interested in Asian petrochemical plants is ICI. "You won't see any ICI petrochemical plants in Southeast Asia," Henderson says, "at least not while I'm chairman."

Nevertheless, some Western companies will want to participate in meeting the huge ethylene demand that is certain to materialize in Asia. Last year, according to Delboy, ethylene demand in the region was about 13 million metric tons. He believes it could reach 24 million metric tons by 2000. That would amount to a tidy 29% of global demand by then.

Asia now is a major ethylene importer, bringing in more than 3 million metric tons in 1990. Most of this came in as ethylene derivatives, largely from the Middle East and the U.S.

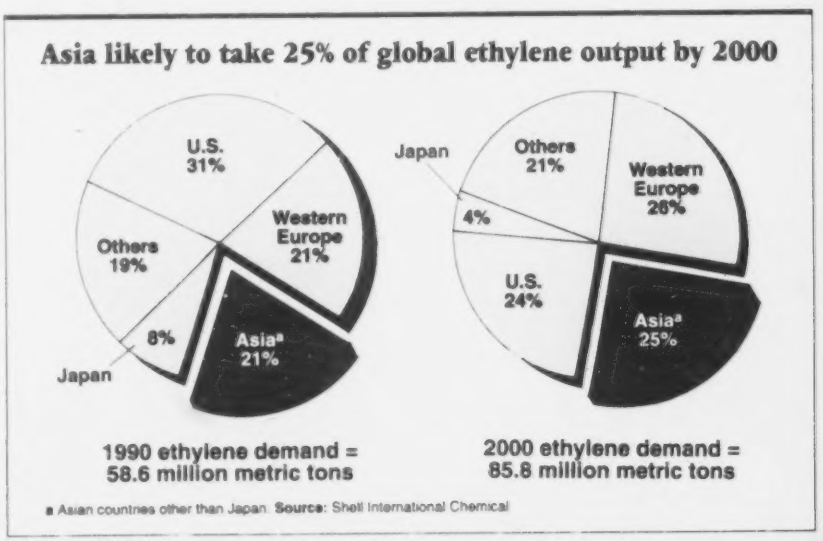
This import deficit, along with the growth in internal demand, provides the stimulus for increasing local output. Western petrochemical companies that fail to participate will pay the penalty, says Delboy.

There's no doubt that world chemical demand patterns will change drastically during the next 10 years, not only for ethylene, but for many other chemicals as well. The one-word reason: Asia.

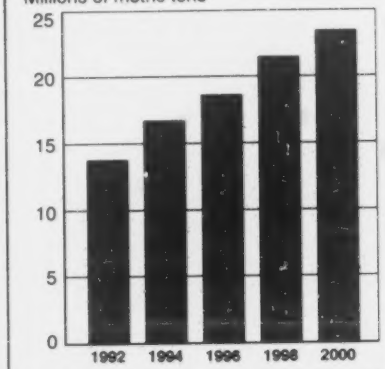
For instance, chemical demand in Asia is expected to grow an average [illegible]% per year between 1990 and 1995, greater than the expected 3.4% world average and much greater than the anticipated 2.7% and 2.5% for North America and Western Europe. And Asia's average annual 5.5% growth rate in chemical demand between 1995 and 2000 also is likely to be the world's fastest.

What does this mean in dollar terms? According to Henderson, it means that by 2000, Asia's chemical market will hit $460 billion (in 1990 prices and exchange rates). It also means that, by 2000—less than eight years away—Asia's chemical market will probably be larger than North America's ($380 billion) and almost as large as all of Western Europe's ($465 billion).

But achieving that success won't be easy for Asia's burgeoning chemical industry. Henderson points out that, right now, the industry is relatively fragmented, at least by the standards of the major Western chemical companies. Although



Asian ethylene capacity up markedly by 2000



[a] Includes present capacity plus future firm and possible additions. **Source:** Shell International Chemical

chemical demand in Asia may be enormous, many of the individual Asian chemical companies ar[e] too small and their markets too localized for them to support the level of research spending that is needed to become a global force. However, with rapidly growing chemical demand right at their doorsteps, most Asian chemical companies have powerful growth ambitions, says Henderson.

Those ambitions could be realized by reorganizing and joining forces, adds Henderson. He points to recent talks between Japan's Mitsui Toatsu and Mitsubishi Petrochemicals as an example. So far, he says, "firm proposals are not evident, to Western eyes at least."

Henderson is right on target. Mitsubishi Petrochemical's Yoshida says that reorganizing is absolutely necessary for Japan's petrochemicals industry if it expects to remain internationally competitive. And he rates as "probable" a large-scale change by 2000.

Japan's ethylene situation provides a good example of why such a change is, indeed, probable. There are 12 Japanese ethylene producers competing for a domestic market of only about 6 million metric tons. This has put a lot of pressure on prices—and profits. In addition, says Yoshida, research and development efforts often overlap and are redundant.

This time, however, reorganizing Japan's petrochemical industry may be different than past efforts, says Yoshida. In the past, Japan's powerful Ministry of International Trade & Finance called most of the shots. This time, says Yoshida, reorganization likely will be left to the individual companies.

Some change has already begun among Japanese chemical companies. One example: Mitsubishi Petrochemical and Mitsubishi Kasai have coinvested in a new 300,000-metric-ton-per-year ethylene plant at Kashima. Completed in June, the plant may be expanded later to 450,000 metric tons.

But it will be China, as well as Japan, that will play a key role in shaping Asia's chemical future and Western chemical companies' response to it. Japan, South Korea, and Hong Kong are investing heavily in China's chemical industry. Recently, China relaxed its import controls and is trading more freely. And because its vast agricultural sector is still relatively primitive, there are great opportunities for agrochemicals.

China's textile industry is growing rapidly and the Japanese already are exporting large amounts of dyes to China to satisfy its requirements. So, too, are South Korea and Taiwan. China's relationship with Taiwan has already become more "pragmatic," says Henderson. And during the next 10 years, both Hong Kong and Taiwan are expected to play a crucial role in China's emergence as a world superpower.

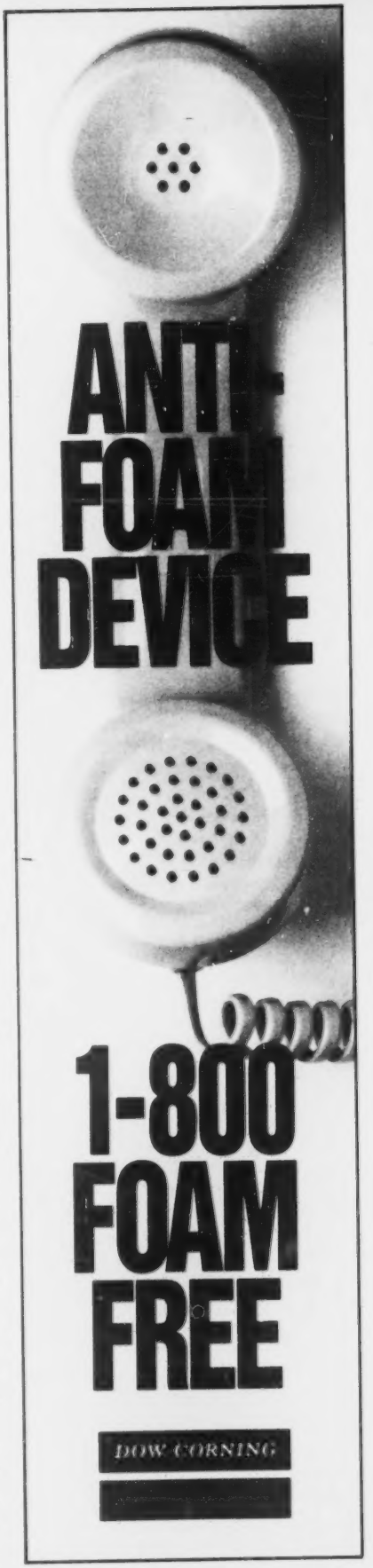
"Overall, I see danger in a restructured and increasingly powerful [Asian] chemical industry being able to consolidate its position in China and the rest of the region," says Henderson. Danger, that is, unless Western chemical companies are fast on their feet.

"You have to be there," says Henderson, referring to China. Recently, ICI has been slowly but steadily putting money into the country.

In addition, Asia's expanding chemical companies will want to invest overseas to broaden their technological base and to increase their share of world chemical trade. Japan, of course, already is doing just that.

In fact, Henderson sees Japan remaining the principal challenge to Western chemical dominance during the next 10 years. Its overseas investment will continue to increase. And, outside their own country, Japanese companies will focus on the high-value-added, high-technology end of the business—primarily pharmaceuticals and biotechnology.

Henderson says what has already been seen in the automotive and electronics industries may well happen in chemicals. Japanese chemical companies, with their products already approved to Japanese standards, will follow wherev-



CIRCLE 20 ON READER SERVICE CARD

er their important customers—the major consumer-oriented Japanese companies—have blazed a trail. Japanese chemical companies are small by Western standards. But they have proven their reliability to their major customers. Thus, says Henderson, it is only natural—and safe—for them to follow their customers wherever they go.

And their customers may, indeed, continue going elsewhere, even more so than they have been ever since the Plaza Accord of 1985—in which nations agreed to coordinate interest and exchange rates—sharply increased the value of the yen and put pressure on Japanese exports.

Yoshida says Japan's domestic "assembly industries" have almost reached their physical limits. As a result, he expects domestic chemical demand in Japan to reach a saturation point as the year 2000 approaches.

So what can Western chemical companies do about what Henderson calls "the challenge of Asia-Pacific?" Based on ICI's 40 years of experience in Japan, he says it is possible for Western companies to overcome the difficulties, to work with Japanese partners, and to benefit from their expertise.

But ICI also has learned that it "can go it alone," says Henderson, not only in the Japanese market, but in other Asian countries such as Taiwan and Malaysia as well. Customers in these countries, he adds, are anxious to get the leading-edge technology and innovative capability of Western chemical companies.

The Asian chemical industry is destined to continue expanding rapidly, regardless of what Western companies may try to do to prevent it, says Henderson. To him, there are two choices: Western chemical companies can either forge alliances with emerging local producers, or they can lose patience and try to erect political and trade barriers that would shut off Western markets to the Asians. "I would suggest that we are too late for the [latter]," he says.

He points out that John Jay, an early U.S. Secretary of State, referred to the Pacific as "the ocean of the future." Henderson is convinced that future is here. □

Environment likely to be factor in trade talks

As more and more countries negotiate international trade agreements, environmental concerns will inevitably become even more closely linked with the customary economic issues. This has been apparent in the stalled Uruguay round of multilateral trade talks. It has become even more obvious in the North American Free Trade Agreement (NAFTA) that Canada, Mexico, and the U.S. recently negotiated.

Loud protests from environmental groups and some politicians notwithstanding, John A. Krol, vice chairman of Du Pont, says that, environmentally, NAFTA "will be a plus from the word go." NAFTA's "green language" is "precedent-setting," he told the recent 2nd World Chemical Congress held in Newport Beach, Calif. And it is the first trade agreement to include sustainable development as a specific objective. To Krol, sustainable development is what the future is all about.

The philosophy of sustainable development recognizes that environmental regulations and the way they are enforced vary from country to country. This is understandable, says Krol. Poverty-stricken countries and those with populations facing starvation have different priorities than wealthy nations. In poor countries, global environmental considerations are likely to get short shrift.

But sustainable development is a concept that seeks to balance environmental and economic issues, he says. The Business Council for Sustainable Development, of which Du Pont and other chemical companies are members, is working to develop this concept into an industrial philosophy.

The basic concept is simple—companies, including chemical companies, must manage their businesses in a way that fulfills the needs and aspirations of a growing world population without compromising the ability of future generations to meet their own needs. It starts, says Krol, from the position that economic and industrial development is essential if people in developing countries are to rise out of poverty. But the second article of faith, as Krol calls it, is that this can be done without destroying the environment on which economic growth ultimately depends.

Because sustainable development is built into NAFTA, Krol believes it can serve as a model for future international trade agreements—in the Western Hemisphere and elsewhere. NAFTA and similar trade agreements, he says, will improve environmental quality. Just as important, environmental standards will become more comparable among the nations involved. And, contrary to many protesters, he believes NAFTA will "level up" Mexican environmental standards to U.S. levels rather than "level down" U.S. standards to present Mexican levels.

There are two reasons for this, says Krol. First, liberalizing trade and markets likely would improve living standards in poorer countries and raise their awareness of environmental problems. And second, more directly, trade agreements increasingly address a range of political issues, including environmental concerns. The European Community's EC-92 initiative is a case in point.

So, too, is NAFTA. According to Krol, it reflects the growing relationship between trade and environmental issues. One significant sign: Representatives from the environmental community are on official trade advisory committees.

Krol believes the freer trade and investment that NAFTA provides will stimulate the flow of private-sector financial, technological, and managerial resources toward solving environmental problems. It is because of this, together with efforts to harmonize environmental regulations throughout North America, that environmental quality will level up, not down.

There is evidence this already is happening, he says. A Business Roundtable survey shows U.S. companies not only comply with Mexican environmental laws, but that many also volun-

Krol: sustainable development is the future

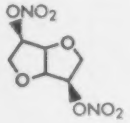
CIRCLE 23 ON READER SERVICE CARD →

Organic Intermediates

for pharmaceuticals, agrochemicals, dyestuffs, flavors, fragrances, photochemicals, etc.

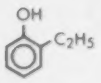
3-Nitro-o-toluic acid
and other isomers

ISDN
Isosorbide dinitrate,
mixtures with lactose,
etc., UPS

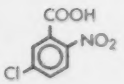


substituted
Indoles
R = CH_3, OCH_3,
$COOCH_3$, Cl, etc.

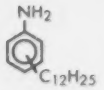
2-Ethylphenol



5-Chloro-2-nitro-
benzoic acid



Dodecylaniline
(isomer mixture)



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Petrochemical capacity rises in Middle East

The traditional petrochemical industries in the U.S., Japan, and Western Europe are going through some rough times, ones that likely will continue to be tough throughout the remainder of the 1990s. And petrochemical plans unfolding in the Middle East won't make things any easier for them.

Countries in the Middle East already have plenty of petrochemical capacity. Nevertheless, they are expanding capacity now and new plants are "waiting in the wings," says Abdullah S. Nojaidi. New output from these plants probably will start hitting world markets during the mid-1990s. That's just when Nojaidi, president of Saudi Arabia's SABIC (Saudi Basic Industries Corp.) Marketing Ltd., expects world petrochemical markets to improve.

Nojaidi told the recent 2nd World Chemical Congress in Newport Beach, Calif., that, "at a minimum," Middle East ethylene and derivatives capacity will double during the decade. Ethylene capacity alone will rise from 3.15 million metric tons in 1990 to almost 4 million metric tons in 1995, then jump to 6.3 million metric tons by the year 2000. By then, the Middle East will account for 6.5% of the world's ethylene capacity, up from 4.9% two years ago.

Coupled with similar expansions in Asia and Latin America, this spells trouble for the petrochemical industries in what Nojaidi calls the triad—the U.S., Japan, and Western Europe. In the 1990s, he expects world ethylene capacity to increase 50%. However, triad capacity will rise by less than a third, although capacity in the rest of the world will double. The triad's share of world ethylene capacity will fall from 66% to 55% during the decade.

Although he sees the world petrochemical picture improving later in the decade, the short-term petrochemical picture is less sanguine. By 1995, world ethylene capacity will increase by one third; demand will rise by less than half that amount. As a result, world petrochemical operating rates will drop from an average 91% in 1990 to only 79% in 1995. "This has to be a worrisome matter for all petrochemical producers," says Nojaidi.

From his vantage point in the Middle East, Nojaidi sees "difficult times" for the world petrochemical industry. Today's prices do not justify investing in the new capacity that will be needed to satisfy market demand by the end of the decade. In the short term, demand is falling, costs are rising, selling prices are low, and the recession—and overcapacity—lingers.

So why the many expansions in the Middle East? Nojaidi contends that long-term petrochemical prospects warrant "timely" capacity additions. The key word, he says, is timely. Most of the new Middle East output will enter world markets late in the decade. By then, says Nojaidi, although market growth rates may still be low, they will be working off a higher base and will be able to absorb the new capacity.

He also believes profits, not volume, will be the key to petrochemical prosperity. This makes him wonder if the old, small, inefficient plants with little or no stake in feedstocks (read Europe) can survive in the more demanding and competitive climate that is coming.

"The Middle East," says Nojaidi, "has paid for its ticket to the party." It certainly has the feedstock. And it has invested heavily in massive feedstock gathering systems, infrastructure networks, and a host of world-scale petrochemical plants.

He believes if a region has the feedstocks, the financial capability, and the nerve to plunge into previously uncharted

Middle East will expand ethylene capacity

Country	Ethylene capacity (thousands of metric tons per year) 1990	1995	2000
Iran	10	735	735
Iraq	150	0	600
Kuwait	0	0	300
Qatar	280	280	600
Saudi Arabia	2,250	2,500	3,000
Turkey	460	460	775
U.A.E.[a]			300
TOTAL	**3,150**	**3,975**	**6,310**
World capacity	64,000	85,000	97,000
Middle East as % of world	4.9%	4.7%	6.5%

a United Arab Emirates **Source:** SABIC Marketing

waters, then it should press its economic advantage. If the Middle East needed any incentive to diversify away from relying on oil revenues alone, it was the European Community's move toward a $10 per barrel energy tax on oil.

In Iran, the petrochemical complex that was destroyed in the Iran-Iraq War is being rebuilt. Other plants are under construction. Oman is in the "advanced planning" stage for an offshore, barge-mounted methanol plant. Kuwait, a major fertilizer producer, is planning an ethane cracker and derivatives complex.

Bahrain has a methanol-ammonia complex, has looked at the possibility of a polypropylene plant, and now is considering an aromatics and derivatives complex as well as a urea plant plus a plant to produce methyl *tert*-butyl ether. And Qatar has in the works a liquefied natural gas complex to serve Asian markets. It also plans to build a new ethane cracker and derivatives complex. The United Arab Emirates may well build an ethane cracker and polyethylene complex.

But Saudi Arabia is, and will remain, the petrochemical champion of the Middle East. The 16-year-old SABIC supplies more than 10 million metric tons per year of petrochemicals to more than 70 countries. Under its current investment strategy, says Nojaidi, SABIC hopes to capture a 4 to 5% share of world chemical markets. Current investment schedules will enable the company to increase its petrochemical capacity from 12 million metric tons annually to 17 million metric tons "in coming years." The goal for later in the decade—20 million metric tons annually.

SABIC is building its fourth ethylene cracker. It will be a variable-feed unit that will enable the company to enter the propylene, butadiene, and aromatics chains of products. Notably, SABIC will produce 200,000 metric tons per year of polypropylene. It also will produce 2-ethyl hexanol and benzene to meet demand at its expanded styrene plant.

The company also is moving up the product chain to produce polyester for fibers and plastic bottles. If all of its expansion plans are completed, SABIC's capacity for its many petrochemical products will be awesome.

Meanwhile, SABIC is looking at overseas direct investment. "We are investigating petrochemical and derivative [investment] opportunities in any of five continents or a combination thereof," says Nojaidi.

Earl Anderson

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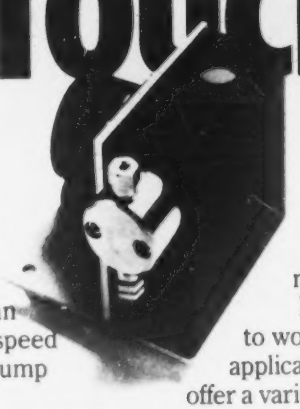

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CHIRAL DRUGS

Stephen C. Stinson,
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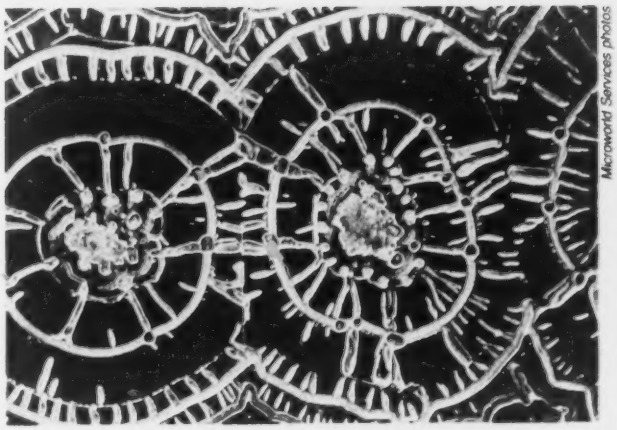


Microworld Services photos

In wake of new FDA guidelines, most drug firms are developing single enantiomers, spawning a "chirotechnology" industry

Development of chiral drugs got a big boost with the Food & Drug Administration's release this summer of its long-awaited guidelines for marketing of these drugs (C&EN, June 15, page 5). Chiral drugs that exist in two or more mirror-image forms (enantiomers) are frequently offered as half-and-half enantiomer mixtures (racemates). The issue is whether drug companies may market such compounds as racemic mixtures or must develop them as single enantiomers. FDA's position is that drug companies have the choice of whether to develop chiral drugs as racemates or as single enantiomers.

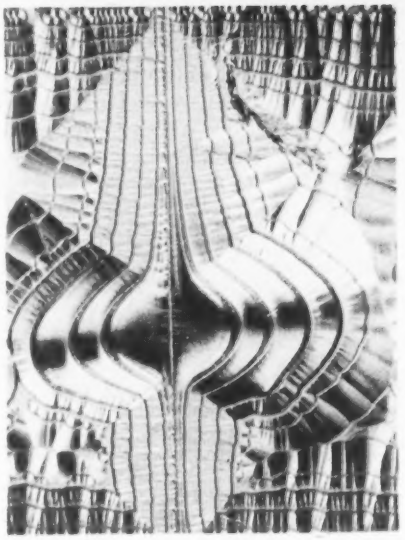
But interpretation of the guidelines will rest with individual FDA reviewers considering particular cases. And under the guidelines, drug companies will have to furnish rigorous justification for FDA approval of racemates. So to avoid unpleasant surprises, most drug companies have decided to develop only single enantiomers. And a few have issued instructions to their research departments to avoid asymmetric molecules entirely.

This evolving regulatory climate in the development of chiral drugs presents many opportunities to drug firms and their suppliers. The chief beneficiary may be the chemist, because resolution of racemates, asymmetric synthesis, and determination of enantiomeric content are chemical activities.

Consultant Enrico T. Polastro of Arthur D. Little International, Brussels, envisions a growing "chirotechnology" industry, whose development he likens to the biotechnology industry. Small startup companies are racing to achieve proprietary resolutions, asymmetric production processes, and enantiomeric intermediates and active drugs. Big drug firms and established fine chemicals producers are adding asymmetric chemistry to their repertoires. And universities are marketing licenses for relevant patents.

Richard L. DiCicco, president of the consulting firm Technology Catalysts International, Falls Church, Va., sees promise in "racemic switches." These are redevelopments of drugs now marketed as racemates to enantiomers. Many racemic drugs have patents that have expired or are running out, and drug companies can patent enantiomers of their racemic drugs to defend

Photomicrographs (these two pages) of crystals of L-ascorbic acid under polarized light



themselves against competition from generic drugs.

If the racemate is already approved by FDA, then less testing is needed to "bridge" the gap to the not-yet-approved enantiomer. DiCicco and others estimate that only four years and $3 million might be needed to get approval for a racemic switch, compared with 10 to 12 years and $240 million for a new chemical entity. At that rate, generic drug companies could steal a march on brand name drug firms by also switching racemates to enantiomers.

Yet another impetus that DiCicco sees for racemic switches is transdermal drug delivery (skin patches). This is because only active compounds would diffuse through the skin. In addition, he points out, patches containing only (S)-(–)-nicotine, for instance, are less irritating than those with the racemate.

Among classes of compounds DiCicco sees as candidates for racemic switches are cardiovascular drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), central nervous system agents, antihistaminics, and prescription drugs being considered for eventual over-the-counter sale.

As for cardiovascular drugs, the other enantiomer of β-adrenergic blocking agents for hypertension often causes the drugs to have side effects, he explains. And a drug containing only the active enantiomer might result in a more potent drug being taken less frequently, therefore enhancing patients' compliance with doctors' orders.

Faster onset of action is the rationale for racemic switches of NSAIDs, DiCicco says. And central nervous system agents are potent drugs that are good candidates for transdermal delivery.

Among antihistaminics, racemic terfenadine causes side effects of dizziness and dry mouth. (S)-Terfenadine, however, may not have these drawbacks. Marion Merrell Dow, Kansas City, Mo., which markets the Seldane brand of racemic terfenadine, has issued a warning that the drug may cause life-threatening irregular heart rhythms when taken with the antifungal ketoconazole or the antibiotic erythromycin. This finding is so new that it is impossible to say whether the arrhythmias would be avoided with the enantiomeric drug.

As for the over-the-counter issue, DiCicco says that FDA is more likely to approve a switch from prescription to over-the-counter if the drug company has in some way developed a form of the drug that requires a smaller dose. An enantiomeric drug may do this.

Some implications of the emerging pharmaceutical chirotechnology are clearly emotional. Doctors are beginning to think that "enantiomeric is better." Sales representatives of one drug company, an industry observer tells C&EN, have urged doctors to prescribe one of its drugs that is not chiral, because "it's not a racemate."

Such marketing techniques also may impress patients. For ibuprofen, contained in Motrin, Nuprin, and Advil, the (S)-enantiomer is the active pain reliever and the (R)-isomer is inactive, but the (R)-isomer is converted to the (S)-isomer in the body. It may or may not be of greater therapeutic benefit that taking pure (S)-ibuprofen achieves higher blood levels of drug sooner. But drug companies may convince the public that S stands for "super," justifying higher prices.

Estimates of the size of the drug chirotechnology market vary. The differences depend on whether enantiomeric intermediates, chiral auxiliaries, bulk active drugs, or finished dosage forms are considered, according to DiCicco.

DiCicco argues that for potential participants in the new chirotechnology, sales of finished dosage forms such as pills or capsules from producer plants is the key number. He puts these chiral drug sales at $18 billion at present, growing to at least $40 billion by the year 2000. He disagrees with estimating the market using the value added by the asymmetry-inducing step.

First, he says, the big drug companies base their decisions to enter or expand on producer plant sales of dosage forms. Second, royalties in licensing agreements are based on a percentage of producer plant sales. Third, as DiCicco puts it, "Quantification of value-added chirality is a tedious analysis that misses the important trends affecting the business fate of chemical sup-

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Chemical "handedness" has its own language

Asymmetric. Completely lacking elements of symmetry. Some asymmetric molecules do not exist as enantiomers, however, and some molecules with simple axes of symmetry do exist as enantiomers (mirror images), so some persons prefer the term "dissymmetric."

Chiral. "Handed," having the characteristic of "handedness," which is having the potential to exist as two nonsuperimposable structures that are mirror images; not synonymous with the terms enantiomerically pure or optically active.

Configuration. Arrangement of atomic groups about a chiral center.

D or L. Absolute configuration of a molecule assigned according to experimental chemical correlation with that of D- or L-glyceraldehyde as the reference compound; often used with amino acids and sugars, but R and S are preferred.

d or *l*. Dextrorotatory or levorotatory according to experimentally determined rotation of the plane of monochromatic plane-polarized light to the right or left; since superseded by (+) or (–).

Diastereoisomers. Stereoisomers with two or more centers of dissymmetry and whose molecules are not mirror images of one another, for example, D-erythrose and D-threose; often contracted to "diastereomers."

Dissymmetric. Lacking an alternating axis of symmetry and so usually existing as enantiomers. Some prefer this to the term "asymmetric."

Enantiomers. Two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

Enantiomeric excess (ee). Percent by which one enantiomer, E_1, is in excess in a mixture of the two; ee = $[(E_1 - E_2)/(E_1 + E_2)] \times 100\%$.

Enantioselectivity. Degree to which a chemical reaction produces one rather than the opposite enantiomer.

Meso compounds. Compounds whose molecules have two or more centers of dissymmetry but also have planes of symmetry and so cannot exist as enantiomers; for example, *meso*-tartaric acid.

Optical activity. Experimentally observed rotation of the plane of monochromatic plane-polarized light by a substance to the observer's right or left.

Optical isomer. Synonym for enantiomer; now disfavored, because most enantiomers lack optical activity at some wavelengths of light.

Optical purity. Percent of one enantiomer in a mixture of the two according to experimentally measured angle of optical rotation; not valid to describe enantiomeric purities determined by other methods.

R or S. Absolute configuration about a dissymmetric center, assigned by drawing the molecule according to specific conventions and finding whether a circle passes through certain atoms surrounding the center clockwise to the right (R, rectus) or counterclockwise to the left (S, sinister).

Racemic. Existing as a racemate, or 50-50 mixture of two enantiomers; also denoted *dl* (discouraged) or (±) (preferred). Racemates also are called racemic mixtures or racemic modifications.

Racemization. Conversion of one enantiomer to a 50-50 mixture of the two.

Scalemic. Existing as a mixture of two enantiomers in which one is in excess; coined in recognition that most syntheses or resolutions do not yield 100% of one enantiomer.

Stereoisomers. Compounds whose molecules consist of the same number and types of atoms with the same connectedness but different configurations.

pliers." Among such trends are the possibility that processes might change and that a certain enantiomeric intermediate might become obsolete. And fourth, an enantiomeric intermediate from a certain supplier might set a purity standard for production of a patented drug and thus determine producer plant values. While the drug patent is in force, the supplier could become very proficient at making the intermediate. When the patent for the drug expires, generic drug firms might find it hard to produce the drug without the intermediate from that supplier.

DiCicco notes that availability of in-

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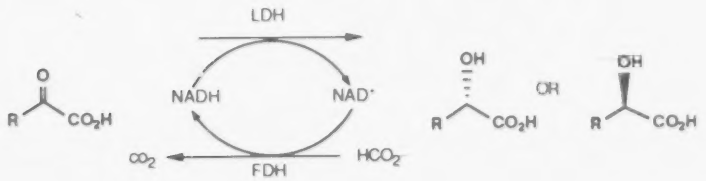

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termediates is often controlled by brand name drug firms and their subsidiaries. For example, in the fall of 1991, Zenith Laboratories, a generic drug company in Northvale, N.J., was planning to bring out a generic form of the cephalosporin antibiotic, cefadroxil. Bristol-Myers Squibb Co.'s patent on cefadroxil had expired.

To formulate and market the drug, Zenith needed bulk cefadroxil manufactured only by Gema of Barcelona, Spain. Gema is a subsidiary of Sandoz of Basel, Switzerland. Gema at first agreed to supply Zenith with the bulk cefadroxil, but at the last moment refused.

At present, the issue is confused, because Zenith, Sandoz, and Bristol-Myers Squibb are in litigation over whether use of the Gema bulk compound infringes Bristol-Myers Squibb patents still in force. This example, says DiCicco, bolsters his point about controlled accessibility to bulk actives and intermediates.

Many drug companies, therefore, are weighing whether to develop racemates or enantiomers and whether to make racemic switches. And many small startup companies dream of becoming the "Genentech of chirotechnology." But consultant William P. Jackson of Chem Systems, London, cautions that these drug companies have to weigh their choices carefully in terms of clinical benefit, marketing advantage, and regulatory considerations.

One question of clinical benefit is whether the enantiomer is superior to the racemate. As a case in point, Jackson cites the β-adrenergic blocking

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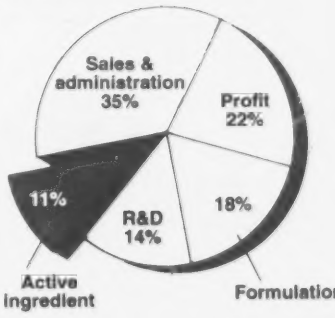

Note: Assumes price of $5000 to $10,000 per kg for patent-protected drug. **Source:** Chem Systems

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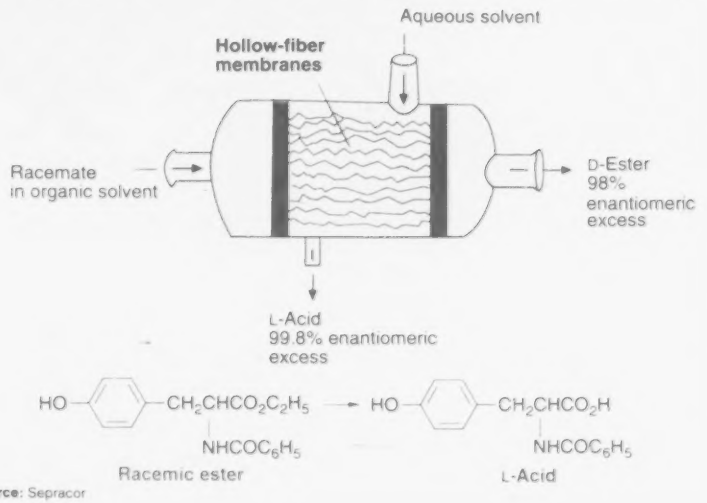


Source: Sepracor

agent labetalol. This drug, designed to treat hypertension, is marketed in the U.S. by Schering-Plough, Madison, N.J.

In 1989, the company introduced (*R,R*)-(–)-labetalol in Japan with the generic name dilevalol. Dilevalol was thought to offer a desired specific antagonism of β_2 receptors in the heart with none of the α-receptor agonism of the racemate. But dilevalol was found to cause liver toxicity and was withdrawn within a year.

Another question Jackson raises is whether drug companies will really reap great profits from racemic switches. For example, the field of NSAIDs—ibuprofen, flurbiprofen, and others—is mature. This means there are so many competing drugs that a racemic switch would have to show some benefit, such as greater safety, to command a higher price. Furthermore, the imminent FDA approval of Pfizer's tenidap, which works by different mechanisms, represents such a significant advance in therapy of inflammatory disease as to make sales estimates for racemic-switched NSAIDs meaningless.

A third factor to consider, Jackson says, is that two enantiomers may have different pharmacological actions. For example, Janssen Pharmaceutica, Piscataway, N.J., is developing nebivolol as a β-blocker for hypertension. But whereas (+)-nebivolol is a β-blocker, (–)-nebivolol is not a β-blocker but is a vasodilating agent. Thus, by alleviating hypertension by two different mechanisms, the racemate may be superior to either enantiomer.

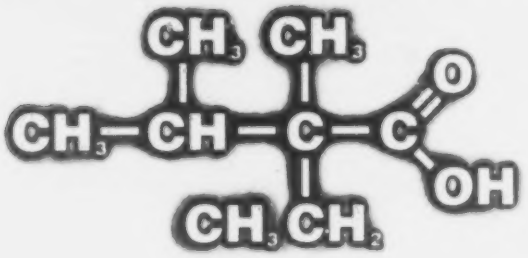
Finally, many industry observers believe that if the potency of an active enantiomer compared with a racemate of active and inactive enantiomers is such that the dose can be cut in half, the patient will benefit. The less drug taken, the less chance of side effects. Jackson cautions that this may not be so.

He poses the hypothetical case of a chiral drug that is degraded by metabolic reactions at a site distant from the asymmetric carbon atom(s). Both enantiomers would be inactivated at the same rate. Therefore, an inactive enantiomer may serve as a sacrificial substrate for degrading enzymes, prolonging the stay of the active enantiomer in the body. To achieve the same therapeutic benefit, the patient would have to take the same dose of costly enantiomer as of cheaper racemate.

But among Jackson's cited marketing advantages, half the dose of the drug, if possible, might be a good selling point with doctors. Another marketing advantage is patent extension. By obtaining or licensing a patent on one enantiomer of its own brand name racemate, a drug company gets an extension of exclusive marketing. It can promote the enantiomer while generic drug firms are limited to the racemate.

Though the cardiovascular calcium-channel blocker nifedipine is not a chiral compound, Jackson cites New York

See what you can make of this.



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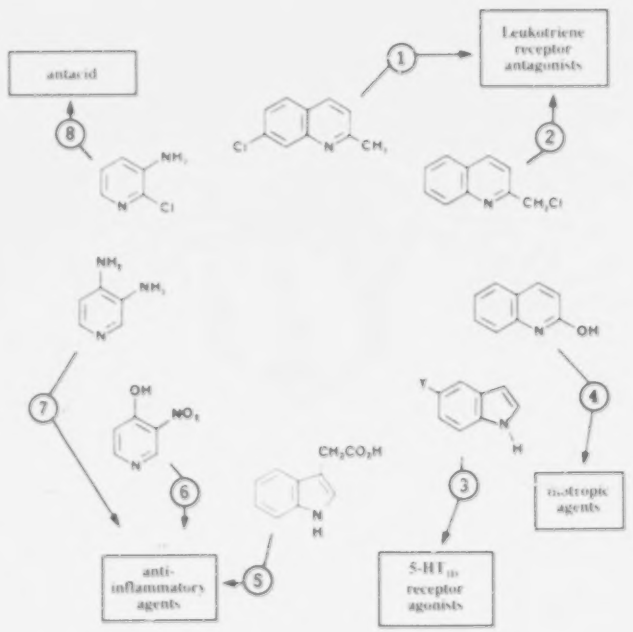

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World enantiomeric drug market is $18 billion

$ Million	1990 sales
Chiral antibiotics	$ 6,360
Captopril	1,501
Enalapril	1,482
Lovastatin	751
Diltiazem	746
Cefadroxil	690
Naproxen	686
Lisinopril	430
Timolol	297
Deprenyl	141
Methyldopa	140
Dexfenfluramine	52
Ethambutol	45
Transdermal nicotine	5
Sertraline	3
Other	4,630
TOTAL	$18,000

Source: Technology Catalysts International

City-based Pfizer's marketing strategy with its Procardia brand of nifedipine as an analogous example of the possibilities with chiral drugs. For many years, Pfizer marketed Procardia to treat angina. Then the company contracted with Alza Corp., Palo Alto, Calif., to design a multilayered, slow-release pill that would deliver nifedipine at a controlled rate by an osmotic mechanism. The new compound was developed.

Patients need take Procardia XL, as Pfizer calls it, only once daily. Pfizer also received FDA approval for hypertension as well as angina as an indication for use of Procardia XL. Now the company advertises to patients that if they take Procardia, they should ask their doctors if they are eligible for Procardia XL. Meanwhile, generic drug companies will be limited to nifedipine in "plain vanilla" for years.

Among the regulatory issues that concern Jackson is the cost of the tests needed to get approval for a racemate or an enantiomer. For a pure enantiomer, barring racemization or inversion in the body, simple chromatography is enough to follow plasma concentrations of the drug and its metabolites. For a racemate, simple chromatography must be followed by chromatography on asymmetric solid supports to learn about each enantiomer. As Jackson points out, such double analysis is costly.

Another of his regulatory concerns is

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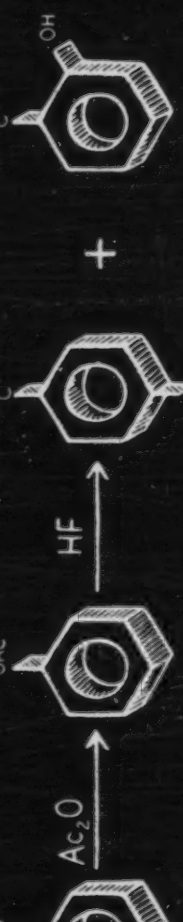

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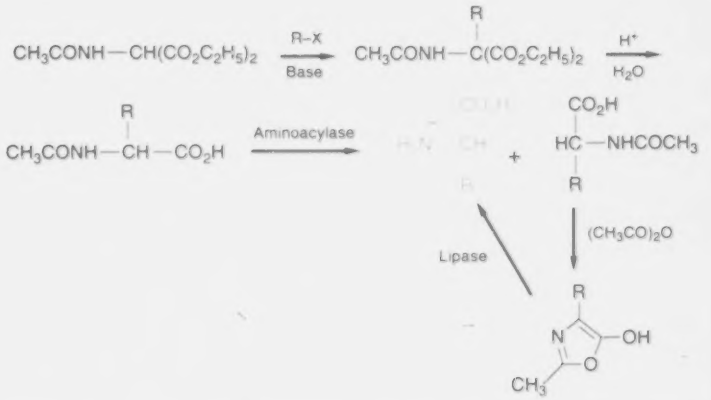
One-pot synthesis drives desired enantiomer formation



precedents in drug development. He cites the introduction of captopril in the enantiomeric form by E. H. Squibb & Sons of Princeton, N.J., as setting the tone for such angiotensin-converting enzyme (ACE) inhibitors. "Subsequent ACE inhibitors such as enalapril and benazepril have been developed in [enantiomeric] form," he says, "and it would be unlikely for a racemic/diastereomeric ACE inhibitor to be approved in the future."

Also important to Jackson is timing in development of a drug when a company decides whether to develop the racemate or one enantiomer. He cites SmithKline Beecham, London, and A. H. Robins Co., Richmond, Va., as examples of two companies who had to do costly backtracking in testing when they switched from racemates to enantiomers.

In the mid-1980s, SmithKline Beecham was developing cromakalim, the front-runner in a new class of compounds called potassium-channel activators. Such compounds have potential to treat angina, hypertension, and asthma, and perhaps glaucoma and impotence as well. The dextrorotatory isomer was found to have side effects, however, so the company switched to what is now called levokalim. The company is still working on FDA approval of levokalim to treat asthma, but lost about four years of clinical testing.

Robins was working on zacopride, a new type of antipsychotic drug that works by blocking type-three receptors of the neurotransmitter 5-hydroxytryptamine (serotonin). But where one enantiomer of zacopride is a $5HT_3$-blocker, the other is an agonist. American Home Products, New York City, acquired Robins in 1989 and transferred zacopride to its Wyeth-Ayerst Laboratories' subsidiary in Philadelphia for continued development as an enantiomer.

As the new chirotechnology industry takes shape to serve the drug industry, A. D. Little's Polastro advises companies to draw lessons from the history of the biotechnology industry. He notes that the biotech industry went through a shakeup in the 1980s when the expectation of quick returns changed to a more realistic estimate of the potential for profits.

Though Genentech and Amgen stand out as success stories of biotechnology, Polastro points out that the number of failures in that industry has greatly exceeded the number of successes. Some companies that did well were able to integrate their originally narrow biotechnological capabilities with a broader set of skills. Others concentrated on particular niches. And still others teamed up with larger companies.

In the chirotechnology industry, two firms that have managed to integrate production of enantiomeric intermediates with broad fine chemicals manufacture are Kanegafuchi Chemical Industry Co., Osaka, Japan, and DSM Andeno of Venlo, the Netherlands, and Elmwood Park, N.J.

Though good estimates are lacking, these two companies are believed to supply almost all of the merchant enantiomeric intermediates to the world drug

industry, worth perhaps $1 billion per year. Another $500 million worth may be made captively by drug companies themselves. Industry observers say that Kanegafuchi is strong in microbiological methods of kinetic resolution and synthesis, whereas DSM Andeno excels in fractional crystallization of diastereoisomeric derivatives and asymmetric organic synthesis.

Ton Wijsman, vice president for DSM Andeno of the U.S., says the company started in chiral intermediates in the early 1980s by supplying *D*-(-)-α-phenylglycine as the side-chain for ampicillin. The company now resolves several hundred metric tons per year of this intermediate.

Since then have come D-(–)-*p*-hydroxyphenylglycine for amoxicillin, D-(–)-S-acetyl-β-mercaptoisobutyric acid for the angiotensin converting enzyme inhibitor captopril, (S)-indoline-2-carboxylic acid for perindopril, and enantiomeric glycidyl *p*-toluenesulfonates for the calcium-channel blocker diltiazem. And along with its growing expertise in the various chemistries, DSM Andeno has developed the capacity to analyze such compounds for enantiomeric excesses, Wijsman says.

One firm that looks to join hands with appropriate partners is Sepracor of Marlborough, Mass. The chirotechnology company has not waited for pioneering drug companies to develop racemic switches of their own brand name drugs but has moved to do so for them and to offer them (or their competitors) licenses. Sepracor also has invented or licensed a panoply of technologies to produce enantiomers generally.

For example, Sepracor has licensed both the asymmetric epoxidation reaction of inorganic chemistry professor Eric N. Jacobsen of the University of Illinois, Urbana-Champaign (C&EN, April 2, 1990, page 20), and the asymmetric dihydroxylation reaction of organic chemistry professor K. Barry Sharpless of Scripps Research Institute, La Jolla, Calif. (C&EN, July 22, 1991, page 19).

Among partnership agreements already reached, Sepracor has signed with Tanabe Seiyaku Co., Osaka, Japan, to supply kinetic enzymatic reso-

These drugs are best candidates for racemic switches

Cardiovascular

Acebutolol	Alprenolol
Atenolol	Betaxolol
Bisprolol	Bopindolol
Bucumolol	Bufetolol
Bufuralol	Bunitrolol
Bupranolol	Butofilolol
Carazolol	Carvedilol
Curteolol	Disopyramide
Dobutamine	Indenolol
Mepindolol	Metipranolol
Metoprolol	Nadolol
Nicardipine	Oxpranolol
Pindolol	Propanolol
Sotalol	Toliprolol
Verapamil	Xibenolol

Central nervous system

Dobutamine	Fluoxetine
Ketamine	Lorazepam
Meclizine	Oxaprotiline
Phenylpropanolamine	Thioridazine
Polycloramphetamine	Tomoxetine
Toloxaton	Viloxazin

Respiratory

Albuterol/ salbutamol	Metaproteranol
	Terbutaline

Anti-inflammatory and analgesics

Cicloprofen	Corticosteroids
Dihydroxythebaine	Fenbuphen
Fenoprofen	Flurbiprofen
Ibuprofen	Indoprofen
Ketoprofen	Minoxiprofen
Pirprofen	Steroids
Suprofen	Triamcinolone

Anticancer

Cytarabine

Antibiotics, antiinfectives, antivirals

Ciprofloxacin	Norfloxacin
Ofloxacin	

Hormones, genitourinary

Benzyl glutamate	Butoconazole
Calcitonin	Estradiol
Fluorogesterone	Gonadorelin
Ketodesogestrel/ estrogen	Norgestrel
Progestin nitanol	Testosterone

Antihistamine and cough/cold

Astemizole	Terfenadine

Source: Technology Catalysts International

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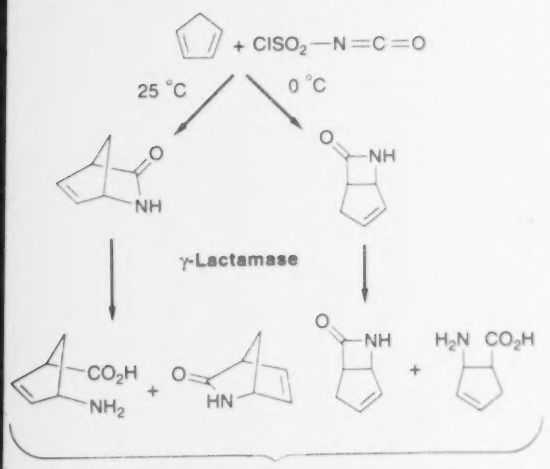
Developmental Intermediates

HPE MEP OCT TYR

Cyclic lactam intermediates open doors to many enantiomeric drugs



lution technology to make an enantiomeric glycidyl derivative as a starting material for diltiazem. It also has licensed technology to Nagase & Co., Osaka, to make *S*-ibuprofen and an intermediate for captopril.

Racemic drugs of other firms for which Sepracor has worked out racemic switches to enantiomers are *S*-atenolol (the β-blocker Tenormin of ICI Pharma), *S*-nitrendipine (the calcium-channel blocker of Miles Laboratories), both *R*- and *S*-fluoxetine (the antidepressant Prozac of Eli Lilly & Co.), *S*-zopiclone (the sedative Imovane of Rhône-Poulenc), *S*-terfenidine (the antihistaminic Seldane of Marion Merrell Dow), *R*-albuterol (the antiasthmatic Proventil of Schering Corp.), *S*-flurbiprofen (the NSAID Ansaid of Upjohn Co.), and *S*-ketoprofen (the NSAID Orudis of Wyeth-Ayerst).

Sepracor says it has already reached one or more agreements with other companies to license these enantiomeric drugs but it is not revealing details of these pacts for now. The company has acquired expertise in all areas of resolution and asymmetric synthesis, tailoring these to achieve the most economical technology to make each compound.

One technique that gets a lot of use is immobilized enzymes in hollow-fiber membrane reactors. By this method, a solution of a relatively nonpolar derivative of a racemic compound in an organic solvent flows through the fiber bundle in a module. Next, an aqueous solvent flows over the outside of the bundle, and an enzyme immobilized in the fiber resin hydrolyzes the derivative enantioselectively to a more polar compound. The more polar enantiomer permeates the membrane, and the aqueous phase carries the hydrolyzed enantiomer away, while the unreacted other enantiomer is collected at the end of the fiber bundle.

Sepracor spokesmen say that single, laboratory-scale, hollow-fiber membrane modules have a capacity of resolving 165 kg per year at a molecular weight of 150. Capacities of whole reactors containing 20 production-scale modules are estimated to be about 100,000 kg per year.

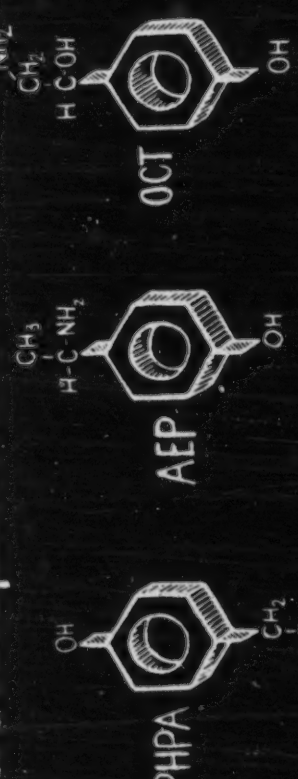
For example, a lipase immobilized in one version of the hollow-fiber membrane hydrolyzes the ethyl ester of *N*-benzoyl-D,L-tyrosine to the free L-acid in 99.8% enantiomeric excess while the D-ester is collected at the end in 98% enantiomeric excess.

In Cambridge, England, Chiros is a new company founded this spring to supply a broad range of synthetic organic and biological resolutions and asymmetric syntheses, mainly to the drug industry. Chiros is the successor firm to Enzymatix, whose chiral business it acquired. Commercial director Andy J. M. Richards says the company is in business both to "solve chiral chemical problems" for customers and to develop racemic switches.

Though intermediates are often specific to single drugs, chemists at Chiros have developed what they believe are generalized methods that open routes to whole classes of compounds. One of these is a one-pot amino acid synthesis. Another involves bicyclic lactam intermediates.

In the amino acid synthesis, the starting material is commercially available diethyl acetamidomalonate. Treatment with base and an alkyl halide produces the acetamidoalkylmalonate, and hydrolysis and decarboxylation yield the

Developmental Intermediates



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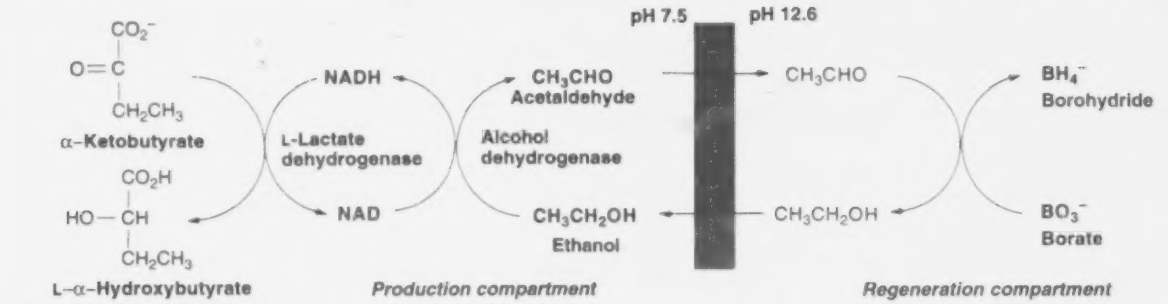
Permeable membrane isolates production medium from rigorous regenerating medium



NAD = Nicotinamide adenine dinucleotide
NADH = Reduced NAD

Source: Bend Research

racemic *N*-acetylamino acid. An aminoacylase selectively cleaves this acid to one enantiomer of the amino acid, leaving the *N*-acetyl derivative of the other enantiomer. Unreacted *N*-acetyl enantiomer is then racemized by conversion to a symmetrical oxazoline, which feeds back to the desired amino acid enantiomer on hydrolysis with a lipase. Thus the process converges on the desired enantiomer without wasting materials.

In the cyclic lactam technology, chlorosulfonyl isocyanate adds to cyclopentadiene at 0 °C to give 7-azabicyclo-[3.2.0]hept-2-en-6-one (the lactam of *cis*-2-amino-3-cyclopentenecarboxylic acid) and at 25 °C to yield 2-azabicyclo-[2.2.1]hept-5-en-3-one (the lactam of *cis*-4-amino-2-cyclopentenecarboxylic acid). Chiros researchers have found microorganisms with γ-lactamase activity. These microbes open one or another lactam enantiomer selectively. The

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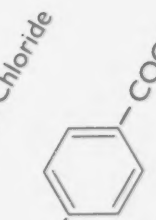

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various enantiomeric aminocyclopentenecarboxylic acids are useful for making nonnatural amino acids, nucleoside analogs, neurotransmitter agonists, and antifungals.

Where Sepracor and Chiros are examples of companies that nurture a stable of chiral technologies and do speculative research and development in search of partners, other firms are seeking niches in the new technology. For example, Celgene of Warren, N.J., has honed enantioselective enzymatic transamination to a fine edge and plans to supply enantiomeric amines as drug intermediates. The company is also developing parallel enzymatic techniques for other compound types.

At Bend Research, Bend, Ore., the emphasis is on selectively permeable ("permselective") membranes. Researchers there devise resolutions and asymmetric syntheses, driving reactions on one side of the membrane by means of complementary reactions in the other compartment.

Newport Synthesis Ireland, Dublin, sells and uses 100-kg quantities of enantiomeric auxiliaries. Enantiomeric auxiliaries are compounds that users bind covalently to substrates to induce asymmetry in later chemical steps. The auxiliaries are then cleaved.

And at Chiros, researchers seek to join enzymatic biotransformations to synthetic organic chemistry. The results are processes that are more economical than either type alone.

Celgene has isolated a number of proprietary transaminases from microorganisms, according to senior vice president Sol Barer. These are available in forms that make either the (R)- or (S)-amine. And transaminases can be used either to synthesize one amine from the corresponding aldehyde or ketone or to resolve a racemic amine by converting the unwanted enantiomer to a carbonyl compound.

For example, synthesis of either enantiomer of α-phenethylamine begins with acetophenone as substrate, a large excess of a low-cost amine donor such as propylamine, and either the (R)- or (S)-version of transaminase enzyme. The transaminase mediates conversion of the reactants to propionaldehyde and an almost 100% yield of (*R*)- or (*S*)-α-phenethylamine in greater than 99% enantiomeric excess based on the amount of acetophenone used.

Sometimes, however, the transaminase

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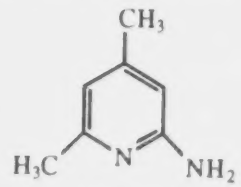
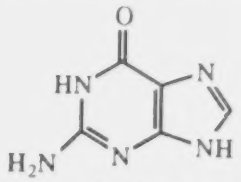
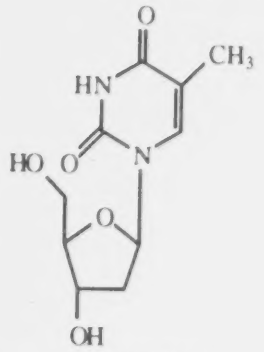
HETEROCYCLIC INTERMEDIATES



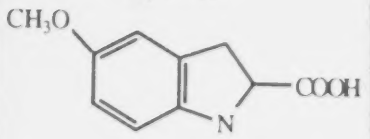
2-amino-4,6-dimethylpyridine



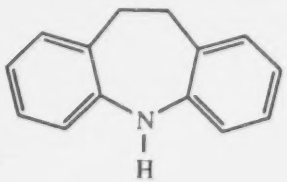
Guanine



Thymidine



5-methoxyindole-2-carboxylic acid



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does not have absolute enantiospecificity for the substrate used. In that case, the resolution mode is preferred.

For example, the (*S*)-aminotransferase gives only 93% enantiomeric excess of (*S*)-1-phenyl-3-aminobutane from 1-phenyl-3-butanone substrate. In the resolution mode, the ketone is first reacted with ammonia and hydrogen catalytically (reductive amination) to give racemic 1-phenyl-3-aminobutane.

Now the racemic amine is combined with the (*R*)-aminotransferase and an amine acceptor such as pyruvic acid. The transaminase catalyzes conversion of the (R)-amine to ketone, leaving the amine enriched in the desired (S)-enantiomer.

The (*R*)-transaminase still lacks complete enantiospecificity, however. So if the reaction were only run to 50% conversion, the (S)-amine would be contaminated with a small amount of unwanted (R)-enantiomer. In actual practice, the reaction is run to 58% conversion. This raises the enantiomeric excess of (*S*)-amine to greater than 99%, though some of the desired (S)-amine is converted to ketone.

There is no real loss, however. All ketone made in the resolution step can be subjected to reductive amination to racemic amine, which is recycled through the enzymatic resolution step and eventually yields virtually 100% of enantiomeric amine based on ketone.

In other developments, Celgene is working on an aldolase technology to condense glycine with, for example, benzaldehyde to make enantiomeric β-phenylserines as side chains for penicillin- and cephalosporin-type antibiotics. Such compounds could be reduced to aminodiols or dehydroxylated to nonnatural amino acids for peptide syntheses.

Celgene seeks to work with customers to supply individual samples of enantiomeric compounds, develop new catalysts and processes, produce kilo to ton lots of intermediates, or furnish biocatalysts and technology for use in customers' own plants. Barer emphasizes that, once an enzyme is in hand, it can be used in conventional chemical process equipment. Also, processes developed in the laboratory can be scaled up to ton lots without changes in technology. Celgene has a license from the Drug Enforcement Administration to make and store arylalkanolamines that may be pharmacologically active.

Scientists at Bend Research also use

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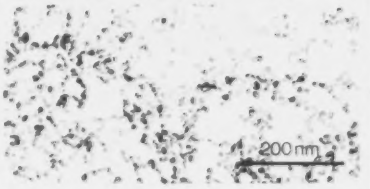

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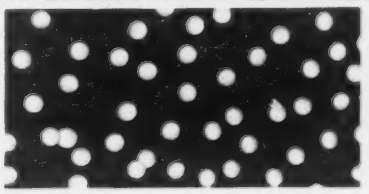

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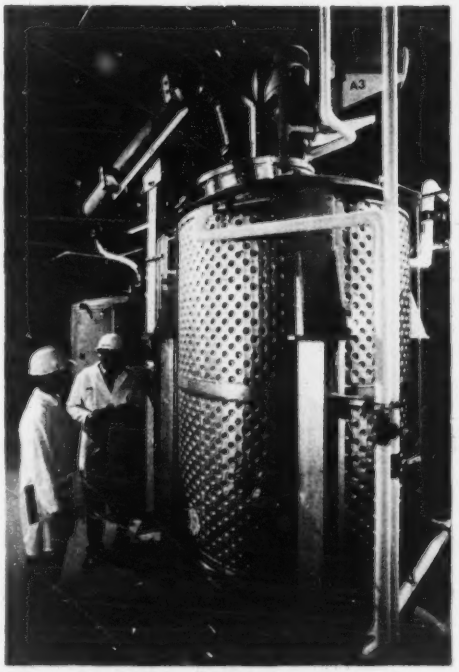
enzymes in their conversions. Because their enzymes sometimes depend on cofactors, they use permselective membranes to separate the delicate enzyme-cofactor chemistry from the strong reagents and severe conditions used to regenerate the cofactors. Development work at the company has been eased by the prior development of many cofactor regeneration reactions by organic chemistry professor George M. Whitesides and coworkers at Harvard University.

For example, the company has developed a reduction of α-ketobutyric acid to L-α-hydroxybutyric acid as a route to drugs through a versatile (S)-1-butene oxide. The reduction is catalyzed by L-lactate dehydrogenase using the reduced form of cofactor nicotinamide adenine dinucleotide (NADH) as the actual reducing agent. NADH is oxidized to NAD. NAD is regenerated to NADH using a complementary oxidation of ethanol to acetaldehyde, mediated by alcohol dehydrogenase.

To keep the regeneration cycle going and to avoid poisoning enzymes in the production compartment, acetaldehyde must be reduced again to ethanol. Bend Research uses sodium borohydride to reduce the aldehyde. But borohydride is a very powerful reducing agent that functions best in much more strongly alkaline solutions than those used for enzymes.

So the Bend Research process separates the borohydride reduction with its pH of 12.6 from the pH 7.5 enzyme compartment by a membrane. Acetaldehyde is the only compound in the production compartment that passes through the membrane to the borohydride side, and ethanol is the only substance on the regeneration side that passes back through.

Bend Research also has developed resolutions of important alcohols based on permselective membranes. In a first



Celgene produces up to ton lots annually of enantiomeric intermediates in these reactors

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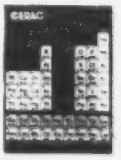

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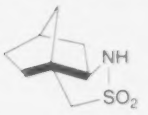
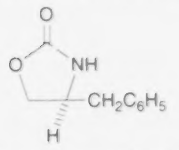
Chiral auxiliaries now available in bulk quantities

Amino acid production



Bornane-10,2-sultam [(2*R*)-isomer shown]

Aldol condensations



4-Benzyl-2-oxazolidinone [(*S*)-isomer shown]

step with racemic 2-norbornenol for example, an (R)-lipase catalyzes esterification of (*R*)-2-norbornenol with butyric anhydride to give (*R*)-butyrate, leaving unreacted (S)-2-norbornenol in greater than 98% enantiomeric excess. The (S)-2-norbornenol passes out through a membrane, which rejects the ester.

But lack of specificity in the lipase leaves the ester in only 78% enantiomeric excess. To rectify this, the Bend Research process next uses the same lipase to hydrolyze the (R)-ester preferentially, also in a membrane process. The (*R*)-2-norbornenol passed by the membrane from the hydrolysis has greater than 98% enantiomeric excess. Alcohols resolved in this way also include β-quinuclidinol, 3-thianol, glycidyl and α-phenethyl alcohols, and mandelonitrile.

Among the chiral auxiliaries available in commercial quantities from Newport Synthesis Ireland are (2*R*)- and (2S)-bornane-10,2-sultam. This compound, first popularized among research chemists by organic chemistry professor Wolfgang Oppolzer at the University of Geneva, Switzerland, finds use in making derivatives of α-amino acid enantiomers.

Also available in bulk are (*R*)- and (*S*)-4-benzyl- and (*R*)- and (S)-4-isopropyl-2-oxazolidinones. These are familiar auxiliaries for enantioselective aldol condensations from the work of organic chemistry professor David A. Evans at Harvard University.

In addition to Chiros and Newport

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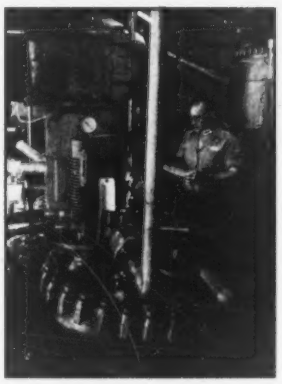

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Chiral drug conferences keep chemists up to date

Conferences have been established in the past few years to keep medicinal chemists current on issues of chirality in the drug industry. To date, three have been held, all in the U.K. The latest, called Chiral '92, was at the University of Manchester, England, March 24–25. The first conference in the U.S., Chiral USA '93, will be held at the Hyatt Regency Hotel, Reston, Va., May 6–7, 1993.

Chiral USA '93, which is sponsored by Spring Innovations of Stockport, England, will consist of a symposium and exposition. Registration will be at the Hyatt Regency on Wednesday afternoon, May 6, and attendance is anticipated to total about 1000, including exhibitors. The program is not yet final, but probably will consist of 20 papers being presented on Thursday and Friday covering such broad subjects as synthesis, resolution, catalysis, and commercial opportunities, and given by academicians, industrial scientists, and consultants.

Those in North America interested in attending Chiral USA '93 should contact Brandon Associates, P.O. Box 1244, Merrimack, N.H. 03054. Both the voice telephone and fax may be reached by calling (603) 424-2035.

Synthesis Ireland, Chiron Laboratories of Trondheim, Norway, is another European company whose enantiomeric products and expertise are available in the U.S. Chiron is represented by Davos Chemical Corp., Englewood Cliffs, N.J. Davos marketing manager Peter A. Demchko says his firm imports compounds made to order in Norway by asymmetric synthesis and/or resolution using synthetic chemical, enzymatic, and fermentation methods.

A company that has found a niche in classical resolution by diastereoisomeric crystallization is Zeeland Chemicals, Zeeland, Mich. The company is the former Hexcel Chemical Products Division, which was acquired by Cambrex Corp. in March. James K. Datson, business development manager at Zeeland, says the firm's main activity is use of enantiomeric acids for resolving racemic amines and of enantiomeric amines for resolving racemic acids.

Genzyme Corp., Cambridge, Mass., is another company that has found lipases able to catalyze difficult but desirable reactions. Scientists at the company recently reported a lipase from the yeastlike microorganism *Candida lipolytica* that hydrolyzes esters of α-methyl-α-amino acids. Such crowded molecular structures often make poor substrates for enzymes. Products of the hydrolyses are such enantiomeric drugs as carbidopa, which potentiates the action of l-dopa in Parkinson's disease, and methyldopa and metyrosine, which are useful for treating hypertension.

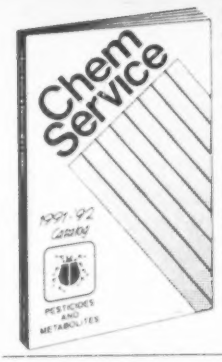
A new enantiospecific technology now appearing on the horizon is asymmetric amplification. This is the use of a catalyst whose chiral moiety is present in low enantiomeric excess, but which gives products that are of much higher enantiomeric excess.

The phenomenon would be of great benefit to the chirotechnology industry, because companies could use less expensive materials of low enantiomeric excess to make intermediates that are more valuable because of their high enantiomeric excess. Until now, though, asymmetric amplification seems to have been explored only by organic chemistry professors H. B. Kagan at the University of Paris-South, Orsay, France, and Nobuki Oguni at Yamaguchi University, Japan, working separately.

For example, Oguni has reported on the reaction of benzaldehyde with diethylzinc, catalyzed by (−)-1-piperidino-3,3-dimethyl-2-butanol (PDB) of low enantiomeric purity, to give (*R*)-(+)-1-phenyl-1-propanol. In six experiments, Oguni varied the enantiomeric excess of the PDB from 3.1% to 59.8%. The resulting enantiomeric excesses of the product ranged from 36% to 94%.

Kagan has a theory of how this could happen. The piperidino compound is a ligand (L) that complexes the zinc, he explains. In this and many other asymmetric catalyst systems, the complex is probably ZnL_2. If the nominally (R)-ligand (L_R) has only 50% enantiomeric excess, then there are actually three molecules of L_R for every one of L_S in the mixture. On average, there should thus be two catalytic complex types, ZnL_RL_S and $Zn(L_R)_2$. If for some reason the meso-catalyst ZnL_RL_S is much less active than its diastereoisomer $Zn(L_R)_2$, then the influence of L_R in the whole process will be greater than that of L_S—in other words, amplified. □

R.S.V.P.



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